## Justification

## National Institute of Allergy and Infectious Diseases

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.

Budget Authority:

| FY 2004 Actual | | FY 2005 Appropriation | | FY 2006 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|---|
| FTEs | BA | FTEs | BA | FTEs | BA | FTEs | BA |
| 1,443 | $4,303,040,000 | 1,507 | $4,402,841,00 | 1,507 | $4,459,395,000 | 0 | $56,554,000 |

This document provides justification for the Fiscal Year 2006 research activities of the National Institute of Allergy and Infectious Diseases (NIAID), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2006 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

**INTRODUCTION**

The National Institute of Allergy and Infectious Diseases (NIAID) is a component of the National Institutes of Health (NIH), which is an agency of the Department of Health and Human Services (DHHS). NIAID supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and other sexually transmitted diseases, illness from agents with bioterrorism potential, tuberculosis, malaria, autoimmune disorders, asthma, and allergies. NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world. The scope of the NIAID research portfolio has expanded considerably in recent years in response to new challenges such as bioterrorism, emerging and re-emerging infectious diseases, and the increase in asthma prevalence among children in this country. The growth of NIAID programs has also been driven by unprecedented scientific opportunities in the core NIAID scientific disciplines of microbiology, immunology, and infectious diseases. Advances in these key fields have led to a better understanding of the human immune system and the mechanisms of infectious and immune-mediated diseases.

**BIODEFENSE: RESPONDING THROUGH RESEARCH**

A terrorist attack on the United States using biological agents, once thought to be a remote possibility, occurred in the fall of 2001, when anthrax spores were sent through the mail. Recent events have raised awareness of both the possibility of a bioterrorist attack and the vulnerability of the U.S. population to such an event. In 2003 and 2004, the toxin ricin was found in an envelope at a postal facility in South Carolina, a U.S. Senate Office Building, and in several jars of baby food in California.

The threat of bioterrorism has created new challenges for medicine and public health. The nation's ability to detect and respond to acts of bioterror requires new and improved countermeasures, including diagnostics, vaccines, and therapies. Although the Department of Defense (DoD) has developed defenses for biological warfare, there are additional concerns that need to be addressed to provide an adequate civilian defense from a bioterrorist attack.

As the lead agency at NIH for infectious diseases and immunology research, NIAID has set research priorities and goals for each microorganism that might be used as an agent of bioterrorism, with particular emphasis on "Category A" agents—those considered by the Centers for Disease Control and Prevention to be the worst bioterror threats. NIAID Category B and C priority pathogens, in general, cause milder disease or fewer deaths than Category A agents and are more difficult to disseminate in populations. NIAID has developed the *NIAID Strategic Plan for Biodefense Research*[1]; the *NIAID Biodefense Research Agenda for CDC Category A Agents*[2]*;* and the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens*[3]. Advances in biodefense research have been rapid and significant, as outlined in the *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report*[4] and the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens Progress Report*[5].

NIAID's biodefense program includes both short- and long-term research targeted at the design, development, and evaluation of the specific public health tools or countermeasures (diagnostics, therapies, and vaccines) needed to control a bioterrorist-caused outbreak. Major biodefense research projects include: ongoing advanced development of products for protecting the public from CDC Category A agents, including better vaccines and drugs for anthrax and smallpox and new vaccines for plague and Ebola; large-scale genomic sequencing of agents, such as the bacteria that cause anthrax and plague, to help identify vulnerabilities and target them with drugs or vaccines; and implementation of major research resources initiated in 2003.

It is anticipated that the large investment in research on biodefense will have many positive spin-offs for other diseases. NIAID research on microbial biology and on the pathogenesis of organisms with bioterror potential will certainly lead to a better understanding of other more common and naturally occurring infectious diseases. In particular, the advancement of knowledge should have an enormous positive impact on our ability to diagnose, treat, and prevent major infectious killers, such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and re-emerging diseases, such as West Nile disease, dengue, influenza, and multi drug-resistant infections. Furthermore, and importantly, the NIAID biodefense research agenda promises to enhance our understanding of the molecular and cellular mechanisms of the immune system. Such knowledge will help in the search for new ways to treat and prevent a variety of immune-mediated diseases, such as type 1 diabetes and rheumatoid arthritis. New insights into the mechanisms of regulation of the human immune system will impact research on cancer, immune-mediated neurological diseases, and allergic and hypersensitivity diseases.

[1] *NIAID Strategic Plan for Biodefense Research,* http://www2.niaid.nih.gov/Biodefense/Research/strategic.pdf, (accessed December 6, 2004).
[2] *NIAID Biodefense Research Agenda for CDC Category A Agents,* http://www2.niaid.nih.gov/Biodefense/Research/biotresearchagenda.pdf, (accessed December 6, 2004).
[3] *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens,* http://www2.niaid.nih.gov/Biodefense/Research/categorybandc.pdf, (accessed December 6, 2004).
[4] *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report,* http://www2.niaid.nih.gov/Biodefense/Research/category_A_Progress_Report.pdf, (accessed December 6, 2004).
[5] *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens Progress Report,* http://www2.niaid.nih.gov/Biodefense/Research/category_bc_progress_report.pdf, (accessed December 6, 2004).

## CATEGORY A AGENTS: DEVELOPMENT OF BIOMEDICAL COUNTERMEASURES AND OTHER RESEARCH PROGRESS

### *Anthrax*

NIAID is aggressively pursing the advanced development of a new anthrax vaccine suitable for civilian populations of varying age and health status. NIAID is developing a next-generation vaccine based on a recombinant form of the anthrax protective antigen (rPA). Two new contracts were awarded to support the production, testing, and evaluation of lots for consistency of rPA vaccine, including a phase II trial.

In the event of a bioterrorism incident, effective therapeutics will be needed to address the immediate health needs of the public. Through the *In Vitro and Animal Models for Emerging Infectious Diseases and Biodefense* program, NIAID is screening existing FDA-approved antimicrobials and immunomodulators for efficacy against inhalational anthrax. Five licensed antibiotics have been selected for study, with ciprofloxacin (Cipro®) as a control. NIAID also is pursuing studies to determine whether the course of antibiotic therapy can be decreased by vaccinating subjects with the rPA vaccine candidates currently under development. In addition, NIAID is supporting the development of two versions of anthrax monoclonal antibodies as potential antitoxin therapies.

NIAID also supports basic research on anthrax. In FY 2004, NIAID-funded scientists determined the three-dimensional structure of the cell-binding component of anthrax toxin, called protective antigen (PA), bound tightly to a target cell surface protein called CMG-2. This discovery offers a precise, finely detailed snapshot of a crucial step in the pathway that allows anthrax toxin to enter human cells. This work provides important new leads for the development of novel antitoxins.

A successful response to a bioterrorist threat requires diagnostics to quickly and efficiently identify the pathogen(s) involved. A team of scientists co-funded by NIAID and DoD have developed an assay to simultaneously detect, in a single sample, three Category A Priority Pathogens, *Bacillus anthracis*, *Yersinia pestis* and *Francisella tularensis*, and one Category B Priority Pathogen, *Burkholderia mallei*.

### *Smallpox and Other Orthopox Viruses*

Smallpox is caused by the variola major virus, a member of the orthopox family of viruses. It is among the most dangerous potential biological weapons because the virus easily spreads from person-to-person, no effective treatment exists, and few people are fully immune to the virus.

The vaccine used to achieve the eradication of smallpox from the human population was based on a live, attenuated strain of vaccinia, a virus related to variola major, the virus that causes smallpox. Previous NIAID-sponsored clinical trials demonstrated that the existing stocks of the smallpox vaccine DryVax® could be diluted five-fold and still elicit a potent immune response. In 2004, another stock of vaccine that was manufactured by Aventis Pasteur in the 1950s and stored as a frozen liquid was shown to elicit a robust immune response, even when diluted ten-fold. The results from these two NIAID-sponsored clinical trials, along with the recent manufacture and purchase of 225 million doses of a cell-cultured version of DryVax® secured under contract by DHHS, indicate that the smallpox vaccine stocks currently available would be sufficient to vaccinate the entire U.S. population in an emergency.

NIAID is vigorously pursing the advanced development of the next generation smallpox vaccine, modified vaccinia ankara (MVA) vaccine, an attenuated poxvirus designed to protect against variola major, the virus that causes smallpox. A 2004 study conducted by NIAID intramural researchers indicated that MVA is nearly as effective as the DryVax® vaccine in protecting monkeys against monkeypox, an animal model of human smallpox. Furthermore, NIAID researchers found that, in addition to protecting healthy mice against a lethal form of the vaccinia virus, MVA protects mice with immune deficiencies. In FY 2004, NIAID awarded two three-year contracts for the production and testing of two MVA vaccine candidates.

In an effort to identify treatments for smallpox infection, over 1,500 compounds, including most of the licensed antiviral drugs, have been evaluated for anti-poxvirus activities in cell culture. The approximately 40 compounds that were active *in vitro* were tested in animal models. The antiviral drug cidofovir was shown to have potential as a therapy for both smallpox and generalized vaccinia, a potential side-effect of smallpox vaccination. In FY 2004, a NIAID-sponsored study indicated that cidofovir applied topically may be more effective than oral or intravenous administration to control vaccinia lesions. NIAID is also evaluating immunotherapy with monoclonal antibodies against vaccinia.

***Ebola and Other Viral Hemorrhagic Fevers***

Viral hemorrhagic fevers are caused by four distinct viral families: arenaviruses, such as Lassa virus; bunyaviruses, such as hantavirus; flaviviruses, such as dengue virus; and filoviruses, such as Ebola and Marburg viruses. As a group, these diseases are characterized by hemorrhaging that begins several days after the sudden onset of high fever, muscle and abdominal pain, and extreme fatigue. NIAID, in cooperation with corporate and Federal partners, has a robust program for the advanced development of a vaccine against Ebola. As part of a cooperative program with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), NIAID scientists at the Vaccine Research Center (VRC) and their collaborators developed an effective vaccination strategy that protects monkeys against Ebola viral hemorrhagic fever. The first phase I trial in humans of a DNA vaccine to prevent Ebola infection has been initiated and is currently fully enrolled. The VRC is also developing an adenoviral Ebola vaccine through a Cooperative Research and Development Agreement (CRADA) with industrial partners. A single dose of this vaccine was recently shown to protect monkeys from Ebola infection. NIAID researchers have also developed candidate vaccines against each of the four dengue virus strains. No treatment for Ebola infection or other hemorrhagic fevers currently exists, although candidate drug screening is under way. NIAID also has supported the evaluation of hundreds of compounds for their *in vitro* activity in models for hemorrhagic fever viruses such as Yellow Fever, Pichinde virus (a surrogate for Lassa), and Punta Toro virus (a surrogate for hantavirus). Approximately 240 compounds were screened in FY 2004.

***Botulism***

Botulinum toxin, the cause of the disease known as botulism, is by weight the most toxic substance known—a dose of less than ten millionth of a gram is fatal to humans about 50 percent of the time. The toxin is produced by the common soil bacterium *Clostridium botulinum*. NIAID investigators recently described the A2 neurotoxin gene cluster in *C. botulinum*.

NIAID supports several initiatives to develop countermeasures against botulinum toxin. Through its *Food and Waterborne Diseases Integrated Research Network*, NIAID funds the development of novel therapeutics to neutralize botulinum toxins in the blood or within neuronal cells. In addition, NIAID supports fast track development of monoclonal antibody-based therapies for

botulinum neurotoxin serotype A by funding the manufacture of monoclonal antibodies that will be used in preclinical and clinical studies. Moreover, a recombinant botulinum vaccine is under development.

***Tularemia***

Tularemia is a potential bioterrorist agent because of its high level of infectivity and its ability to be aerosolized. Inhalation of as few as ten bacteria can cause disease. NIAID is collaborating with USAMRIID to develop clinical laboratory methods for working with tularemia, and with the DoD Joint Vaccine Acquisition Program to conduct planned safety and efficacy clinical trials of a newly manufactured, modernized version of the Soviet LVS tularemia vaccine. Proposals for the coordinated development of research tools needed to identify and evaluate new candidates for a safe, effective, general-use tularemia vaccine were recently solicited, and awards are scheduled to be made in FY 2005.

***Plague***

Plague is caused by the bacterium *Yersinia pestis*. Historically, plague has occurred in sporadic but severe epidemics, including the "Black Death" that occurred in Europe during 14$^{th}$ century. The bacterium is usually transmitted from infected animals to humans by insects, especially fleas. Inhalation of *Y. pestis* can cause a pneumonic form of the disease, which can be transmitted from person to person and is nearly always fatal, if untreated.

One of the barriers to development of countermeasures against plague has been the lack of animal models that could allow studies of *Y. pestis* transmission and pathogenesis. In FY 2004, NIAID scientists developed a flea-to-mouse model of flea-borne transmission of plague. The model was used to test a recombinant plague vaccine candidate developed by USAMRIID. The vaccine, called F1-V, was found to protect mice against a flea-borne plague challenge.

In FY 2004, NIAID awarded a contract to develop recombinant plague vaccine candidates, manufacture and test the vaccines, and conduct clinical studies in healthy populations. In addition, NIAID established a cooperative program with USAMRIID to test FDA-approved antibiotics for efficacy against pneumonic plague in monkeys.

**NIAID CATEGORY B AND C PRIORITY PATHOGENS AND TOXINS: RESEARCH PROGRESS**

NIAID Category B and C priority pathogens, in general, cause milder disease or fewer deaths than Category A agents and are more difficult to disseminate in populations. Category B agents include: inhalational bacteria, toxins, food- and water-borne pathogens, and arthropod-borne viruses. Category C agents include all emerging infectious disease threats. Significant progress has been made since the January 2003 release of the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens*[6]. In June 2004, the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens Progress Report*[7] was released.

Several NIAID-sponsored research programs relevant to Category B pathogens and toxins have been established and are currently under way, including work to develop a vaccine against the toxin ricin. In addition, NIAID-funded researchers have identified and cloned multiple proteins from the Category B pathogen *Coxiella burnetii*, the causative agent of Q fever, that react with

[6] *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens*, http://www2.niaid.nih.gov/Biodefense/Research/categorybandc.pdf, (accessed December 6, 2004).

[7] *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens Progress Report*, http://www2.niaid.nih.gov/Biodefense/Research/category_bc_progress_report.pdf, (accessed December 6, 2004).

infection-derived antibodies. These proteins are logical candidates for future vaccines against Q fever.

Food and water are potentially important routes for the dissemination of infectious agents by terrorists. NIAID is expanding its capacity to conduct translational research, including the development of diagnostics, vaccines, and therapies for food- and waterborne diseases. NIAID's programs have begun to yield results that should aid in ultimately developing medical countermeasures to combat these diseases. For example, in FY 2004, NIAID-supported research led to the determination of the entire genetic sequence of *Cryptosporidium hommis*, a common contaminate of public water systems. In addition, proteins from *Vibrio cholerae*, the causative agent of cholera, which are recognized by the human immune system when it mounts a protective response, were identified. Furthermore, transgenic mice engineered to express defensin, an antibiotic peptide found in the human intestine, were shown to be highly resistant to *Salmonella typhimurium*, a dangerous and sometimes fatal food-borne bacterium. Finally, a protocol is under development for a phase I study of a candidate *Shigella flexneri* vaccine.

**UNDERSTANDING, ASSESSING, AND ENHANCING HOST IMMUNITY**

NIAID supports research into both innate and adaptive immune responses, which may provide insights that lead to the development of new or improved interventions against agents of bioterror. Innate immune responses are nonspecific defense mechanisms that come into play soon after a pathogen enters the body (e.g., physical barriers such as the skin, chemicals in the blood, and immune system cells that attack foreign cells in the body). In contrast, adaptive immune responses are highly specific to a pathogen and are carried out by white blood cells called B and T cells. NIAID-supported scientists recently identified a mechanism through which the body alerts its immune system to an invading pathogen. They discovered that uric acid, which is released from dying cells, acts as a powerful signal to activate the earliest pathways of immunity. This discovery may lead to new immune-boosting strategies, including strategies that could be of particular benefit if biotechnology advances lead to engineered or modified threat organisms.

Findings by other researchers supported through NIAID's *Innate Immune Receptors and Adjuvant Discovery Program* indicate that the magnitude and type of immune response to vaccination can be manipulated, for example, by altering the route of immunization. These discoveries will aid in designing more effective vaccines for specific pathogens.

NIAID continues to strengthen its portfolio of research aimed at understanding the host immune system and how it responds to agents of bioterror through a broad range of initiatives. For example, NIAID supports basic, clinical, and applied research on human immune responses to all categories of agents of bioterror through its eight *Cooperative Centers for Translational Research on Human Immunology and Biodefense*. Little is known about why people respond differently to pathogens. To address this knowledge gap, NIAID recently awarded six contracts to identify associations between specific immune responses and variations in genes. Furthermore, NIAID awarded 14 contracts to support the *Large-Scale Antibody and T Cell Epitope Discovery Program,* which is aimed at identifying the regions (epitopes) of select infectious agents that elicit immune reactions.

**RESEARCH CENTERS AND OTHER SPECIALIZED RESEARCH RESOURCES**

In 2003, NIAID created a nationwide network of eight multidisciplinary *Regional Centers of Excellence (RCE) for Biodefense and Emerging Infectious Diseases Research.* These centers

conduct research on NIAID Category A–C agents designed to advance the development of diagnostics, therapeutics, and vaccines. In June 2004, NIAID announced that it intends to fund the creation of two additional RCEs; awards are anticipated for 2005.

In 2003, NIAID supported the creation of two National Biocontainment Laboratories (NBLs). These facilities, when built, will include new Biosafety Level 4 (BSL-4) laboratory space designed to safely contain the most dangerous pathogens known. NIAID also funded the construction of nine Regional Biocontainment Laboratories (RBLs). These facilities, distributed geographically throughout the country, will include new BSL-3 laboratories. In 2004, NIAID announced a new initiative to develop five to eight additional RBLs; awards are anticipated in FY 2005. In addition to the construction of extramural biocontainment facilities, NIAID has begun the construction of three intramural research facilities that will house biocontainment laboratories. NIAID has also initiated a program to fund the renovation and upgrade of existing biocontainment laboratories.

NIAID has made a significant investment in the genomic sequencing of microorganisms that are relevant to national biodefense. By the end of FY 2004, the complete genome of at least one strain of each Category A, B, and C agent has been sequenced through the combined efforts of public and private investigators. Projects are ongoing to acquire the genomic sequences of at least one additional strain of every bacterium, virus, or protozoan on the list of Category B and C pathogens.

NIAID also supports programs that supply vital research tools to biodefense researchers nationwide and provide a range of resources for preclinical testing of new therapies and vaccines in both cell culture and animal models, including nonhuman primates. In FY 2004, several new animal models for Category A-C Priority Pathogens were developed: two new animal models for viral hemorrhagic fevers, a model of flea-borne plague transmission, and two models for West Nile virus.

**Future Directions in Biodefense Research**

In FY 2006, NIH will continue to expand its research related to potential agents of bioterrorism as part of a broad research agenda involving other agencies within DHHS and DoD. Since 2001, NIAID has launched dozens of biodefense research initiatives, all with the overarching goal of facilitating the creation and advanced development of new therapies, diagnostic tests, and vaccines that will allow the United States to mount a successful medical and public health response to a biological attack on the civilian population, should such a terrible event occur. Research will include countermeasures for existing naturally occurring threats, as well as ones that will guard against the risk of biotechnology advances leading to engineered or modified organisms that could evade current medical countermeasures or enhance their virulence.

Continued cooperation and coordination with the pharmaceutical industry will be vital to the success of the biodefense research program as scientific advances are translated into new countermeasures that will be available in an emergency. To this end, Project BioShield legislation, which was signed into law in July 2004, will help expedite the conduct of NIH research and development on medical countermeasures. Shortly after the signing of the Project BioShield legislation, NIAID announced several new initiatives to expand biodefense research and product development. These include *Therapeutics for CDC Category A Agents: BioShield Accelerated Countermeasure Development,* which will support projects and studies needed to obtain investigational new drug (IND) status for countermeasure candidates; two initiatives

aimed at the development of countermeasures against botulism: *Neutralizing Monoclonal Antibodies for Type A Botulinum Neurotoxins*, which will support fast track development of monoclonal antibody-based therapy for botulinum toxin by funding manufacture of monoclonal antibodies for evaluation in preclinical and clinical studies, and *Recombinant Type E Botulinum Neurotoxin Vaccine*, which will support fast track development of the recombinant botulinum neurotoxin serotype E vaccine through support of the manufacturing of clinical grade lots for evaluation in preclinical and clinical studies; and *Protecting the Immune System Against Radiation: BioShield Accelerated Product Development.* In FY 2006, NIAID will continue to use its BioShield authorities to launch new biodefense initiatives. *Drug Development Resources for Antiinfectives* will support and accelerate development of antimicrobials by providing preclinical drug development resources to the scientific community and industry partners. Other biodefense initiatives to be unveiled in FY 2006 include *Development of a Multivalent Recombinant Botulinum Vaccine* and *Cooperative Research Partnerships for Biodefense,* which will aim at accelerating the development of promising medical countermeasures through preclinical and early clinical stages by means of collaborative partnerships with academia and industry.

In FY 2006, NIAID will continue to promote research projects through NIAID-supported genomic networks that take advantage of the availability of microbial and human genome sequence data and examine the functional analyses of gene and protein expression on a genomic scale. Also in FY 2006, using funds from the Public Health and Social Services Emergency Fund (PHSSEF), NIAID will continue to collaborate with OPHEP on advance research initiatives which will inform the development and acquisition of potential BioShield medical countermeasures including methods for measuring radiation exposure, prevention of exposure injuries and the development of methods or drugs to restore injured tissue. In addition, FY 2006 PHSSEF funds are proposed for the support of a new initiative to develop medical countermeasures against chemical agents used as weapons of mass destructions.

NIAID will also continue to support initiatives aimed at garnishing a greater understanding of the immune response to pathogens including those that emerge or re-emerge. In FY 2006, NIAID will launch the initiative *Innate Immunity to NIAID Category B Protozoan Pathogen-Associated Molecular Patterns* and will continue to support the following FY 2005 initiatives: *Modeling Immunity for Biodefense*, which supports multi-disciplinary centers to develop novel or improved highly predictive mathematical models that simulate immune function; *Disabling Innate Immune Evasion: New Attenuated Vaccines*; and *Immune Function and Biodefense in Children, Elderly and Immunocompromised Populations*.

**CONFRONTING INFECTIOUS DISEASES**

Infectious diseases have afflicted humanity since its inception, and they will continue to be a menace as long as man and microbes coexist. For example, since AIDS was first recognized in 1981, this emerging disease has spread relentlessly throughout the world. It now threatens to surpass in total fatalities both the "Black Death" of the 14th century and the influenza pandemic of 1918-1919, two other emerging infections that each killed tens of millions of people. In the past five years alone, West Nile and monkeypox viruses emerged in the United States, while Asia experienced an unprecedented number of human infections with avian influenza viruses and the emergence of a new infectious disease, SARS.

## MAJOR INTERNATIONAL KILLERS

### *HIV/AIDS*

The human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), destroys a person's immune system over many years, making the infected individual highly susceptible to multiple infections and certain cancers. Despite recent progress in treatment and prevention, HIV/AIDS continues to exact an enormous toll throughout the world. Estimates on the scope of the HIV/AIDS pandemic are profoundly sobering. At the end of 2003, an estimated 40 million people worldwide were living with HIV/AIDS, five million people worldwide were newly infected with HIV, and three million people with HIV/AIDS had died in the last year[8]. To help turn the tide of the global HIV/AIDS pandemic, NIAID established research collaborations with international colleagues in more than 50 countries focused on HIV vaccine development and other prevention activities, therapeutics, and care for the HIV-infected person. These collaborations already have yielded important results, notably in developing methods to reduce mother-to-child-transmission of HIV.

NIAID-supported investigators have made critical discoveries about the basic biology of HIV and the immune response to HIV infection, which have led to the development of therapies that suppress the growth of the virus. Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication, why the host immune response fails to control the infection, and how reservoirs of virus persist in the body despite highly active antiretroviral treatment (HAART). NIAID continues to search for more scientific information about how the virus attacks the body and how the body defends itself, which is critical for identifying additional targets for therapeutic interventions and vaccines.

*Science Advances in HIV/AIDS Research*

HIV Patients Get Long-Term Boost with Short, Intermittent Drug Regimen. NIAID scientists demonstrated that brief, widely-spaced courses of the experimental immune-boosting drug interleukin-2 (IL-2) allow people with HIV to maintain near normal levels of CD4+ T cells, a type of immune cell, for long periods. These data provide strong evidence that IL-2 therapy, which can be self-administered by patients, could be an important adjunct to a type of HIV treatment called highly active antiretroviral therapy (HAART).

Weekly Cycles of Once-Daily Antiviral Drugs Could Reduce Cost of HIV Treatment. NIAID researchers have shown that it may be feasible to treat HIV-infected patients with a simple, once-daily regimen of anti-HIV drugs given in pre-planned, 7-day-on, 7-day-off cycles. This approach, used with well-chosen drug regimens in settings where patient adherence is high, could be a powerful and cost-effective tool in treating HIV-infected individuals.

Investigational DNA Vaccines for HIV Show Promise. NIAID scientists at the Vaccine Research Center have developed a novel DNA vaccine for HIV directed at the three most globally important clades or subtypes. The vaccine incorporates genetic material from clades A, B, and C, which cause about 90 percent of all HIV infections worldwide. The genes used for the development of this vaccine were *env*, which encodes a protein on the surface of HIV, and *gag*, *pol*, and *nef*, which encode internal proteins. Initial tests of combinations of the DNA segments

[8] Joint United Nations Programme on HIV/AIDS (UNAIDS), *UNAIDS 2004 Report on the global AIDS epidemic*, Switzerland, 2004.

carrying the HIV genes showed promising immune responses in non-human primates. Such tests also suggest that a multigene, multiclade HIV DNA vaccine is feasible because the immune responses to individual genes in the vaccine are not reduced when combined with one another. This candidate vaccine is the first multigene, multiclade vaccine to enter human clinical trials.

HIV Protein Vif Subverts Host Cell Antiviral Defenses. NIAID-supported investigators have uncovered a novel pathway through which HIV evades the counterattack mounted against it by a host cell. An HIV protein called Virion Infectivity Factor (Vif) had previously been shown to be essential for viral replication. Vif works by suppressing the anti-HIV activity of APOBEC3G, a host protein. To better understand how Vif counteracts the antiviral function of APOBEC3G, NIAID-supported investigators isolated and identified the host proteins with which Vif associates during infection. Their studies revealed that the interaction of Vif, APOBEC3G, and the host protein Cullin5 form a complex known as Cul5-SCF. In turn, Cul5-SCF induces the degradation of APOBEC3G. The identification of interventions that either modulate levels of APOBEC3G or block its interaction with Vif through the Cul5-SCF complex could lead to new and innovative strategies for treating HIV infection.

GB Virus C Infection Inhibits HIV Replication. HIV patients are commonly coinfected with other pathogens, such as the hepatitis C virus (HCV). Coinfection generally contributes to AIDS mortality. In contrast, men infected with both HIV and an apparently harmless virus called GB virus type C (GBV-C) for at least five years were three times less likely to die than HIV-positive men who did not have GBV-C. NIAID-supported scientists investigated the cellular mechanisms for the protective effect of GBV-C on HIV positive individuals. They found that when a type of immune cells called peripheral blood mononuclear cells (PBMCs) were infected with both HIV and GBV-C, the levels of cellular chemical messengers called chemokines were increased. In addition, they found an inverse correlation between chemokine levels and HIV replication. Moreover, they observed that the chemokine receptor CCR5, which is a co-receptor of some strains of HIV, was decreased on the surface of the HIV/GBV-C coinfected PBMCs. The elucidation of the mechanism through which GBV-C prolongs the survival of individuals infected with HIV may lead to the identification of targets for the development of novel therapeutics and vaccines to combat HIV/AIDS. In addition, this research provides clues as to why the course of HIV infection is so variable among individuals.

*Future Directions in HIV/AIDS Research*

NIAID will continue to support a broad array of domestic and international HIV/AIDS research programs that seek to increase basic knowledge of the pathogenesis, natural history, and transmission of HIV disease, and to support research that promotes progress in its detection treatment, and prevention. In addition, NIAID will continue to support basic research that seeks to increase understanding of the biology of HIV and how the immune system responds to it.

In FY 2006, NIAID will restructure all of its HIV/AIDS clinical trials networks. This reorganization, designed in response to both the changing face of the AIDS epidemic and evolving scientific challenges, will enable NIAID and its many collaborators to effectively pursue research for safe, effective, and affordable drugs and other therapeutic strategies, preventive strategies, and HIV vaccines. In addition, it will enable NIAID to more effectively respond to global research needs, particularly for people living with and most at risk for HIV/AIDS. The major scientific priorities that will be addressed with this new clinical trials matrix will be: 1) developing HIV vaccines; 2) translating research insights into therapeutic

products to treat HIV disease; 3) optimizing clinical management of HIV/AIDS, including co-infections and other HIV-related conditions; 4) developing microbicides to prevent HIV acquisition and transmission; 5) preventing mother-to-child transmission of HIV; and 6) developing other methods of HIV prevention.

NIAID supports all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate HIV vaccines. As of September 2004, NIAID had conducted or initiated, in collaboration with academic researchers and with industry co-sponsorship, over 70 vaccine trials, including 66 Phase I, 4 Phase II, and 1 Phase III trials. These studies involved over 11,000 volunteers, 51 vaccines, and 14 adjuvants. NIAID has a number of new vaccine candidates in the preclinical pipeline, and four to eight are expected to enter Phase I studies in the next two years. These candidate vaccines will be evaluated in animals and then in early safety studies in humans.

In FY 2006, NIAID will continue to support HIV vaccine clinical trials, including a phase III clinical efficacy trial to evaluate a novel HIV vaccine strategy commonly referred to as "prime-boost." The trial, which began enrolling volunteers in 2004, is being conducted in Thailand in conjunction with the U.S. Army Medical Research and Materiel Command of the DoD. NIAID also will support several ongoing initiatives that promote the development of HIV vaccines, including the *Innovation Grants for Approaches in HIV Vaccine Research Program, HIV Vaccine Research and Design Program*, the *Integrated Preclinical/Clinical AIDS Vaccine Development Program (IPCAVD),* and the *HIV Vaccine Design and Development Teams (HVDDT).* In FY 2006, both the IPCAVD and HVDDT programs are slated to be recompeted.

NIAID supports the discovery and development of effective therapies for HIV/AIDS and associated complications and co-infections by facilitating and expediting research on highly promising candidate agents and novel therapeutic concepts. In FY 2006, NIAID will recompete the initiative *Novel HIV Therapies: Integrated Preclinical/Clinical Program,* which supports the discovery, development, and evaluation of innovative concepts for the treatment of HIV infection.

***Tuberculosis***

The bacterium that causes tuberculosis (TB), *Mycobacterium tuberculosis* (Mtb), is estimated to infect two billion people, or about one-third of the world's population. Five to ten percent of infected people will develop active TB disease sometime in their lifetimes. Each year, approximately eight million new cases of active TB occur, and approximately two million people die of the disease[9].

*Science Advances in Tuberculosis Research*

A Tuberculosis Vaccine Ready for Testing in Humans has Shown Promising Results in Two Different Animal Models. While a vaccine for tuberculosis has been in use for more than 60 years, its clinical utility is restricted to preventing pediatric complications of tuberculosis, with limited and variable impact on adolescent or adult pulmonary disease, which are the dominant modes of disease transmission. NIAID-funded scientists have reported encouraging results in animals with a new candidate TB subunit vaccine. The vaccine displayed potent immune responses in mice and guinea pigs and protected against challenge with a virulent strain of TB. Human clinical trials of this candidate vaccine began early in 2004.

[9] World Health Organization, *Tuberculosis, Fact Sheet No. 104*, Switzerland, 2004.

*Future Directions in Tuberculosis Research*
In FY 2006, NIAID will continue to promote and support a broad range of research on TB through its intramural research program and research initiated by individual investigators, as well as through NIAID-supported research programs, such as the *Tuberculosis Research Unit*, *National Cooperative Drug Discovery Groups for Tuberculosis*, and *TB Vaccine Testing and Research Materials*. NIAID will also continue to contribute to the Global Fund to Fight AIDS, TB, and Malaria.

***Malaria***
Malaria is one of the major killers of humans worldwide, threatening the lives of more than one-third of the world's population. Caused by a single-celled parasite and transmitted by mosquitoes, malaria causes an estimated 300 million acute illnesses each year and more than one million deaths[10]. The threat posed by malaria is growing, primarily because of the spread of drug-resistant strains and insecticide-resistant mosquitoes, changing weather patterns, and limitations of the medical and public health infrastructure in many endemic areas.

*Science Advances in Malaria Research*
Combining the Antimalarial Drug Sulfadoxine-Pyrimethamine with other Antimalarial Drugs Reduces Treatment Failure Rates. Resistance to antimalarial drugs, especially chloroquine, the frontline treatment for more than 50 years, has become a major problem in Africa. Affordable and effective treatment options are limited, and signs of resistance are beginning to appear with sulfadoxine-pyrimethamine **(**SP), a widely used second-line antimalarial agent. Combining antimalarial drugs with different mechanisms of action can improve treatment efficacy and may delay the spread of drug resistance. NIAID-supported investigators compared the effectiveness of treating patients with malaria with the antimalarial drug SP alone or combined with either artesunate (AS) or amodiaquine (AQ). The rate of relapse was higher among patients treated with SP alone than among those treated with the SP plus AQ combination. These results indicate that the SP plus AQ combination is a more effective treatment than SP alone and may both impede the spread of drug-resistant parasites, as well as prolong the therapeutic lifespan of current antimalarial drugs.

*Future Directions in Malaria Research*
In FY 2006, NIAID will continue to promote and support malaria research through research initiated by individual investigators, as well as through targeted initiatives that aim to develop new therapeutics, new and improved diagnostics, and a vaccine to prevent infection. NIAID will continue to pursue the systematic implementation of its *Malaria Vaccine Plan*[11], which was designed to accelerate research leading to the development of malaria vaccines.

## EMERGING AND RE-EMERGING INFECTIOUS DISEASES

***Severe Acute Respiratory Syndrome***
Severe Acute Respiratory Syndrome (SARS) is the first severe, newly emergent infectious disease of the 21st century. SARS is a respiratory illness caused by a newly identified virus named SARS coronavirus (SARS-CoV). The disease emerged in late 2002 and spread to several

[10] World Health Organization, *Malaria, Fact Sheet No. 94*, http://www.who.int/mediacentre/factsheets/fs094/en/ (accessed on December 4, 2004).
[11] *NIAID Research for Malaria Vaccine Develop*ment, http://www.niaid.nih.gov/dmid/malaria/malvacdv/toc.htm, (accessed December 30, 2004).

countries in early 2003. The World Health Organization reported 8,096 cases, including 774 deaths worldwide[12].

*Science Advances in SARS research*

SARS Animal Models Developed. NIAID scientists and their collaborators developed several animal models for SARS, including mouse, hamster, and non-human primate models. They also determined that the transfer of immune sera from infected mice and hamsters, which contained antibodies against SARS-CoV, protected uninfected animals from SARS infection. These observations suggest that vaccines that induce antibodies which neutralize the SARS-CoV and immune-based therapeutic and preventive measures with anti-SARS antibodies are likely to be effective against the SARS-CoV. In other efforts to evaluate the potential of immunotherapy, NIAID-funded researchers have developed a human monoclonal antibody that reduces viral replication in mice and protects them against SARS-CoV challenge.

Three Candidate SARS Vaccines Developed. NIAID researchers have developed three candidate SARS vaccines, a DNA vaccine and two live attenuated virus vaccines. When mice vaccinated with the DNA vaccine were exposed to SARS-CoV, viral replication was reduced one-million fold. NIAID scientists at the VRC have begun a Phase I clinical trial to study early stage safety and immune response of this DNA vaccine candidate in humans. The attenuated live virus vaccines were made by inserting the gene encoding the SARS-CoV Spike (S) protein into two existing vaccines, modified vaccinia Ankara (MVA), which was initially developed as a vaccine against smallpox and has an excellent safety record in humans, and a recombinant attenuated human parainfluenza virus 3 (BHPIV3), which is an experimental vaccine against HPIV3, a virus that can cause respiratory illness in children. The MVA and BHPIV3 vaccines act to transport the SARS-CoV S gene into the body. The MVA/S vaccine was tested in mice and the BHPIV3/S vaccine in African green monkeys. Both experimental vaccines protected the immunized animals from infection with SARS-CoV.

*Future Directions in SARS Research*

In FY 2006, NIAID will continue to support basic and clinical research on SARS through its intramural and extramural programs. Basic research is supported through *Biodefense and Emerging Infectious Diseases Research Opportunities* and *NIH Investigator-Initiated Small Research Grants.* In FY 2006, product development, including vaccine, drug and immunotherapeutic development, will be supported through *Cooperative Research Partnerships for Biodefense, the Small Business Biodefense Program* and the *NIAID Advanced Technology Program.*

***West Nile Virus***

West Nile virus (WNV) first emerged in the Western Hemisphere in 1999, in New York City. The virus, transmitted by mosquitoes, has spread rapidly throughout the Americas. By 2004, the virus had been found in birds and mosquitoes in every state except Alaska and Hawaii. People who contract WNV usually experience no symptoms or only mild symptoms—fever, headache, body aches, skin rash, and swollen lymph glands. However, if WNV enters the brain, it can cause life-threatening encephalitis or meningitis. Currently, there are no drugs to treat the virus and no vaccines available to prevent infection.

[12] World Health Organization, *Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003,* http://www.who.int/csr/sars/country/table2004_04_21/en/ (accessed December 3, 2004).

*Science Advances in West Nile Virus research*

Clinical Trial of Experimental West Nile Virus Treatment. In FY 2004, NIAID expanded a Phase I/II clinical trial of an experimental WNV treatment to about 60 sites throughout the United States and Canada. The purpose of the study is to determine whether WNV-infected individuals given antibodies to the virus are better able to fend off the severe symptoms of WNV, such as encephalitis, that contribute to the deaths of some of the individuals who become infected. The antibody preparation, Omr-IgG-am™, contains high levels of anti-WNV antibodies that were isolated from patients who recovered from WNV disease.

*Future Directions in West Nile Virus Research*

NIAID supports basic and clinical research on WNV, including research to develop and test vaccines, drugs and other therapeutic treatments, and improved diagnostics. For example, in FY 2006, NIAID will continue to support the development and testing of experimental WNV vaccines. NIAID also will continue to support the Phase I/II clinical trial of Omr-IgG-am™.

***Influenza and Other Respiratory Diseases***

In the United States, influenza and pneumonia are the leading infectious causes of mortality and are ranked seventh among all causes of death. Annual influenza outbreaks (epidemics) in the United States typically occur between December and March and cause approximately 36,000 deaths each year[13]. Influenza can also cause global outbreaks of disease in which worldwide morbidity and mortality rates significantly increase (pandemics). The potential for a pandemic exists when new strains of influenza have emerged to which the human population has little or no prior immunity, and the virus acquires the ability to quickly spread from person to person and cause severe illness and death. Information about the influenza virus and NIAID-supported influenza research is detailed on the NIAID website *Focus on the Flu*[14].

*Science Advances in Influenza and Other Respiratory Diseases Research*

*[See Story of Discovery on page 20]*

Production and Clinical Testing of Investigational Avian Influenza Vaccines. In early 2004, a highly virulent strain of avian influenza, H5N1, re-emerged in southeast Asia, killing 32 of 44 people infected[15]. Although the people in this outbreak were primarily infected through direct contact with birds, experts are highly concerned that the H5N1 may mutate to become highly infectious to humans and cause pandemic influenza. In FY 2004, NIAID awarded two contracts to support the production and clinical testing of an investigational vaccine based on the H5N1 strain. If a pandemic of H5N1 avian influenza were to occur in humans, the availability and production of such a vaccine on a commercial scale could be used to protect laboratory workers, public health personnel at risk and, if needed, the general public. In addition, NIAID supported the production of an investigational vaccine based on an H9N2 strain of avian influenza virus that has infected humans and has the potential to trigger a modern-day pandemic.

*Future Directions in Influenza and Other Respiratory Diseases Research*

NIAID supports the majority of Federally funded influenza research, including pandemic preparedness research outlined in the DHHS *Pandemic Influenza Response and Preparedness*

[13] CDC, *Influenza: Questions and Answers: the Disease*, http://www.cdc.gov/flu/about/qa/disease.htm (accessed December 3, 2004).
[14] NIAID, *Focus on the Flu*, http://www2.niaid.nih.gov/newsroom/focuson/flu04/, (accessed December 3, 2004).
[15] World Health Organization, *Situation updates - Avian influenza* (accessed December 4, 2004).

*Plan*[16]. In FY 2006, NIAID will continue to support through its intramural and extramural programs both basic and applied research on influenza virus biology, epidemiology, pathogenesis, immunology, and the development of new and improved influenza diagnostics, antiviral drugs, and vaccines. In FY 2006, NIAID plans to expand the *Pandemic Preparedness in Asia* contract, which supports surveillance and characterization of avian influenza viruses with pandemic potential in the live bird markets in Hong Kong. NIAID will also launch in FY 2006 the initiative *Pandemic Preparedness: Production of H7 Inactivated Influenza Vaccines* for production of vaccine that will be used for clinical trials to evaluate its safety and immunogenicity. In addition, NIAID, in collaboration with multiple partners, will continue to support the *Influenza Genome Sequencing Project,* which conducts influenza genomic sequencing and rapidly provides the sequence data to the public, enabling scientists to further study how influenza flu viruses evolve, spread, and cause disease.

[16] DHHS, *Pandemic Influenza Response and Preparedness Plan*, http://www.hhs.gov/nvpo/pandemicplan/ (accessed December 7, 2004).

**Story of Discovery — Confronting Influenza: Responding through Research**

Every year in the United States, more than 200,000 people are hospitalized and about 36,000 people die from influenza, commonly referred to as the flu, and its complications[1]. In addition to the human cost, influenza exacts a tremendous toll economically. Recent estimates put the cost of influenza epidemics to the U.S. economy at between $71 and $167 billion per year[2].

Influenza, which is caused by a virus, is a classic example of a re-emerging disease; it is not a new disease, but it continually changes. The virus also can change suddenly through the recombination of two or more influenza viruses. When this happens, it usually is a "dead end" infection that cannot readily transmit between humans. However, if a virus acquires the capability to spread efficiently from person to person, the result can be a fast-moving and deadly pandemic, such as the influenza pandemic that occurred in 1918-1919, which killed 20-50 million people worldwide[2]. That virus is thought to have arisen through the recombination of an avian influenza strain with a human strain.

Until recently, flu researchers believed that avian influenza A viruses could not infect humans directly. Scientists thought that an avian flu virus would first need to infect another animal, such as a pig, before being transmitted to humans. In 1997, for the first time, scientists learned that avian influenza viruses could infect humans directly when the avian influenza virus strain called H5N1 infected 18 people, six of whom died[3]. In 2004, the H5N1 virus circulated in East Asia; as of October 25, 2004, there had been 44 reported cases of people infected with the virus and 32 people had died[4]. Fortunately, it is not easily transmitted between people.

***Fighting Back***

NIAID has responded to the public health threat posed by influenza virus by supporting research to monitor circulating and emerging flu strains, understand how new strains evolve, and develop diagnostics, treatments, and preventive strategies.

Preparedness planning involves surveillance of influenza virus activity. NIAID-supported scientists conducting surveillance of influenza strains in Asia investigated the genetic origin and spread of a highly pathongenic avian influenza virus strain, H5N1, which caused outbreaks in poultry and humans in 2003 and 2004[4]. Their findings indicate that a dominant form of the virus emerged and was sustained in domestic ducks in southern China and may have then been spread by wild birds to other parts of Asia[5]. The fact that H5N1 may now be endemic in poultry in Asia indicates that it has developed an entrenched ecological niche and may be difficult to eradicate.

If this avian influenza strain or another highly pathogenic avian influenza strain were to mutate and become transmissible between humans, it would not be recognized by the human immune system and could lead to widespread infection, illness, and death. Therefore, an arsenal of treatments and preventive strategies is needed to prevent a worst case scenario from happening.

An innovative strategy developed by a team of scientists supported by NIAID may lead to the development of novel ways to treat, and perhaps prevent, influenza infection. The scientists used a technique known as RNA interference to shut down the expression of targeted influenza virus genes[6]. The scientists designed specific short interfering RNA (siRNA) molecules to target two influenza proteins that are essential for infection. These siRNAs, when given to mice by injection or aerosol before or after viral infection, blocked virus production in the lungs and effectively prevented and treated influenza infection.

The most effective way to prevent the flu is through vaccination; however, it can take four to six months to produce vaccine in large amounts. If a flu strain with pandemic potential does evolve, scientists will need to act quickly to generate a vaccine against the new virus. Recently, NIAID-supported investigators developed a technology, plasmid-based reverse genetics, which has the potential to dramatically decrease the time it takes to produce a flu vaccine[7]. Using this technique, the researchers were able to custom make, in only four weeks, a vaccine reference strain of the H5N1 avian virus. Previous attempts to produce a vaccine against this highly lethal virus had failed because the virus could not be grown in chicken eggs, a necessary step in the current production of flu vaccine. NIAID-supported investigators have begun clinical trials of the H5N1 vaccine strain made using reverse genetics to evaluate its safety and efficacy in humans.

[1] U.S. CDC, *Influenza Questions and Answers: the Disease*, http://www.cdc.gov/flu/about/qa/disease.htm (accessed December 4, 2004)

[2] WHO, Influenza, *Fact Sheet No. 211,* http://www.who.int/mediacentre/factsheets/fs211/en/ (accessed December 4, 2004).

[3] World Health Organization, *Assessment of risk to human health associated with outbreaks of highly pathogenic H5N1 avian influenza in poultry*, (accessed December 4, 2004).

[4] World Health Organization, *Situation updates - Avian influenza* (accessed December 4, 2004).

[5] Li KS et al., Genesis of a Highly Pathogenic and Potentially Pandemic H5N1 Influenza Virus in Eastern Asia. Nature 430: 209-13, 2004.

[6] Qing Ge et al., Inhibition of Influenza Virus Production in Virus-Infected Mice by RNA Interference. Proc. Natl. Acad. Sci. U.S.A. 101: 8676-8681, 2004.

[7] Webby et al., Responsiveness to a Pandemic Alert: Use of Reverse Genetics for Rapid Development of Influenza Vaccines. Lancet 363: 1099-1103, 2004.

***Transmissible Spongiform Encephalopathies***

Transmissible spongiform encephalopathies (TSEs) are a family of neurodegenerative disorders that affect many mammals, including humans. These diseases include scrapie, which primarily affects sheep; bovine spongiform encephalopathy or "mad cow disease," which affects cattle; chronic wasting disease (CWD), which affects deer and elk; and Creutzfeldt-Jakob disease, which affects humans. TSEs are untreatable and invariably fatal diseases of the brain. TSEs are characterized by the presence within the brain of abnormally shaped versions of protein molecules called prion proteins, which are associated with the tissue damage observed in these diseases. Although the precise nature of TSE infectious agents remains unclear, it is known that the abnormal form of the prion protein can convert normal prion protein molecules to the abnormal form, and thus has the potential to be the infectious agent.

*Science Advances in Transmissible Spongiform Encephalopathies Research*

Persistent Scrapie Infection is Likely Due to Cell-Specific Factors that May Serve as Therapeutic Targets. Normal prion protein is expressed in a wide variety of tissues, yet conversion of normal prion protein to the TSE form appears to be restricted primarily to cells of the nervous and lymphoid systems. In order to determine why some cell types are more resistant to TSE infection than others, NIAID scientists developed a tissue culture system that allows them to monitor both acute and persistent abnormal prion protein (or PrP-res) formation. They demonstrated that, while any cell type can make new PrP-res following exposure to TSE infectivity, only some cell types go on to become chronically infected and make PrP-res persistently. This suggests that there are cell-specific factors that determine the susceptibility of a cell to chronic TSE infection. These factors, once identified, could be useful in designing effective anti-TSE therapeutics.

*Future Directions in Transmissible Spongiform Encephalopathies Research*

In FY 2006, NIAID will continue to support TSE research through its intramural and extramural research programs. The NIAID TSE research agenda is focused on four areas: understanding the infectious agents of TSEs; defining how TSEs are transmitted among animal species and across species barriers; developing diagnostic tests; and developing therapies.

***Hepatitis***

Hepatitis refers to a group of liver diseases caused by a diverse set of viruses: hepatitis A, B, C, D, and E viruses. Infection with hepatitis viruses causes liver inflammation, tissue damage and dysfunction. Both hepatitis B virus (HBV) and hepatitis C virus (HCV) cause chronic infection. In the United States There are approximately 1.2 million HBV carriers[17] and approximately 2.7 million HCV carriers[18].

*Science Advances in Hepatitis Research*

Researchers Identify Better Hepatitis C Treatment for People with HIV. NIAID-supported scientists determined that that the preferred treatment for HCV, peginterferon and ribavirin, is safe for people who are also infected with HIV. Moreover, this treatment proved superior for the treatment of HCV in HIV-coinfected persons when compared with the previously accepted treatment, standard interferon and ribavirin.

[17] U.S. Centers for Disease Control and Prevention, *Frequently Asked Questions About Hepatitis B,* http://www.cdc.gov/ncidod/diseases/hepatitis/b/faqb.htm (accessed December 3, 2004).

[18] U.S. Centers for Disease Control and Prevention, *Hepatitis C Fact Sheet,* http://www.cdc.gov/ncidod/diseases/hepatitis/c/cfact.pdf (accessed December 3, 2004).

*Future Directions in Hepatitis Research*
In FY 2006, NIAID will continue to conduct and support basic and clinical research on the hepatitis viruses. The new initiative *Non-Biodefense Partnerships: Vaccines for Hepatitis C* will be launched to stimulate industry participation in the development of vaccines for hepatitis C. In addition, NIAID will continue to support several ongoing projects, including the *Hepatitis C Cooperative Research Centers*, which conduct multidisciplinary HCV research, and the *Animal Models for the Prevention and Treatment of Hepatitis B and C* initiative.

### *Antimicrobial Resistant Microbes*

Antimicrobials have transformed the treatment of many infectious diseases that were killers only a few decades ago. Over time, however, many pathogens have developed resistance to these powerful drugs. All major groups of pathogens—viruses, fungi, parasites, and bacteria—can become resistant to antimicrobials. Due to the emergence and spread of antimicrobial resistance, several bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus*, vancomycin-resistant *Enterococcus*, multi-drug-resistant *M. tuberculosis*, and penicillin-resistant *Streptococcus pneumoniae* are difficult to treat and have negative clinical outcomes and increased treatment costs.

*Science Advances in Antimicrobial Resistance Research*
Understanding How Resistance Develops. Originally appearing only in hospital settings, methicillin-resistant *S. aureus* (MRSA) has now emerged as a community-acquired infection. To determine the origins of MRSA strains circulating within the community, NIAID-supported investigators isolated bacteria from a high-risk population and conducted genetic analysis. The researchers found 58 percent of MRSA infections were caused by strains traceable to hospitals or long-term care facilities. Infections linked to injection drug use, however, were not linked to health care facilities. Therefore, while hospitals appear to remain the main source of MRSA in the community, the presence of other genetically diverse strains indicates that some MRSA strains now originate from the community.

*Future Directions in Antimicrobial Resistance Research*
In FY 2006, NIAID will support a new initiative called *Drug Development Resources for Antiinfectives*. NIAID also plans to continue research through an initiative launched in FY 2005, *Sepsis and Community Acquired Pneumonia: Partnerships for Diagnostics Development* to support development of diagnostic technologies for early detection for pathogens that cause hospital-acquired diseases, including drug-resistant respiratory and systemic infections. NIAID will also continue support for several antimicrobial resistance-related research networks, including the *Network on Antimicrobial Resistance in S. aureus*. Furthermore, NIAID will continue collaborations with industry for the development of novel products to address resistant bacterial infections in healthcare settings.

## OTHER INFECTIOUS DISEASES

### *Sexually Transmitted Infections*

Sexually transmitted infections (STIs) can be caused by a variety of viruses, bacteria, and parasites. More than 25 STIs have been identified, and each year they affect more than 15 million people in the United States[19]. STIs can lead to infertility, complications in pregnancy, cervical cancer, low birth weight, congenital/perinatal infections, other chronic conditions such

[19] U.S. Centers for Disease Control and Prevention, *Tracing the Hidden Epidemics: Trends in STDs in the United States 2000*, http://www.cdc.gov/nchstp/dstd/Stats_Trends/Trends2000.pdf (accessed December 3, 2004).

as neurosyphilis, and increased risk of HIV infection. Treatment and prevention of STIs have become critical global and national health priorities because of their devastating impact on women and infants and their inter-relationship with HIV/AIDS.

*Science Advances in Sexually Transmitted Infections Research*

Once-Daily Antiviral Treatment with Valacyclovir Reduces the Risk of Transmission of Genital Herpes to Uninfected Partner. A randomized controlled clinical trial conducted by NIAID-supported scientists demonstrated that once-daily antiviral suppressive therapy with valacyclovir significantly reduced the risk of transmission of genital herpes from an infected partner to an uninfected heterosexual partner. This was the first time an antiviral had been shown to reduce the risk of transmission of a sexually transmitted infection.

Universal Chlamydia Screening of Adolescent Males on Entry to a Detention System Is a Cost-Effective Prevention Strategy. NIAID intramural researchers and their collaborators determined that universal chlamydia screening of young males on entry to a detention system was the most cost-effective strategy to prevent pelvic inflammatory disease in their recent and future partners. Screening detained male youth using a urine-based test provides a public health opportunity to significantly reduce chlamydia infections in youth at risk for STIs.

*Future Research Directions in Sexually Transmitted Infections Research*

In FY 2006, NIAID will continue to support basic and clinical research studies on mechanisms of pathogenesis of STIs and prevention strategies for the control of these infections through the NIAID-funded *Sexually Transmitted Diseases Cooperative Research Centers* and the *Sexually Transmitted Infections Clinical Trials Group*, as well as several other related initiatives.

***Enteric Diseases***

Bacterial and viral infections of the gastrointestinal tract can lead to diarrheal disease as well as chronic conditions such as ulcers and stomach cancer. In the United States, diarrhea is the second most common infectious illness, accounting for one of every six (16 percent) of all infectious diseases[20]. Data compiled by the World Health Organization indicate that diarrheal diseases account for 15 to 34 percent of all deaths in some countries and worldwide cause more than two million deaths per year[21].

*Science Advances in Enteric Diseases Research*

Mechanisms by which *Helicobacter pylori* Evades the Host's Immune Response. Infection with *H. pylori* is a major risk factor for developing peptic ulcer disease, stomach cancer, and primary gastric B cell lymphoma. NIAID researchers have identified mechanisms that may aid in the ability of the bacteria to colonize the stomach and persist for decades. Most *H. pylori* strains secrete a vacuolating toxin (VacA), which has been implicated as an important virulence factor in the pathogenesis of peptic ulceration and gastric cancer. New evidence demonstrates that VacA suppresses the increase in numbers of *H. pylori*-specific immune cells. These effects may contribute to the capacity of *H. pylori* to evade the adaptive immune response and establish persistent infection.

*Future Directions in Enteric Diseases Research*

In FY 2006, NIAID will continue to support research aimed at understanding, preventing, and treating enteric diseases through a wide array of initiatives, including investigator-initiated

[20] Mead PS et al., Food-Related Illness and Death in the United States. Emerg Infect Dis 5: 607-625, 1999.
[21] World Health Organization. *Communicable Diseases 2002: Global Defence Against the Infectious Disease Threat. Geneva*, Switzerland, 2003.

efforts and targeted programs, such as the *Food and Waterborne Diseases Integrated Research Network* and the *Cooperative Research Partnerships for Biodefense.*

***Lyme and Other Insect-Borne Disease***

Ticks, mosquitoes, lice, and fleas often spread viral, bacterial, and parasitic diseases. Lyme disease, an infection caused by the bacterium *Borrelia burgdorferi*, remains the most prevalent tick-borne infectious disease in the United States. The U.S. incidence of reported cases of Lyme disease declined 10 percent from 2002 to 2003, from 23,763 cases in 2002 to 21,273 in 2003[22].

*Science Advances in Lyme and Other Insect-Borne Diseases Research*

Key to Survival of the Bacterium that Causes Lyme Disease. NIAID-supported investigators discovered that two bacterial proteins, outer surface protein A (OspA) and B (OspB), are essential for the colonization and survival of *B. burgdorferi* in ticks, thereby playing a crucial role in the transmission of Lyme disease to humans. Other studies have shown that if ticks are fed on mice immunized against OspA or OspB, or if ticks are permitted to feed on mice that have been treated with antibodies specific for OspB, the colonization of *B. burgdorferi* in the ticks is significantly impaired. This suggests that the development of vaccines that stimulate production of antibodies specific for OspA or OspB in wildlife populations may be an effective strategy for preventing the spread of Lyme disease.

*Future Directions in Lyme Disease Research and Other Insect-Borne Diseases Research*

In FY 2006, NIAID will continue its long-standing commitment to research on Lyme disease, ehrlichiosis and Rocky Mountain spotted fever through both intramural and extramural research. Studies will include research on vectors and reservoirs, pathogenesis of disease; immune mechanisms in the host; animal models for basic and applied research; and improved diagnosis, treatment and prevention of disease.

***Fungal Diseases***

Severe, sometimes life-threatening, systemic infections caused by fungi have long been recognized in all age groups in all parts of the world. Treatment of fungal infections requires prolonged administration of relatively toxic drugs, which are sometimes ineffective, even in otherwise healthy patients. Fungal infections are recognized as a major cause of morbidity and mortality in patients with an impaired immune system. In addition, advances in modern medicine involving immunosuppression have contributed to the increase in fungal diseases in hospital settings.

*Science Advances in Fungal Diseases Research*

Monoclonal Antibodies Protect Against the Fungus *Histoplasma capsulatum.* The fungus *H. capsulatum* is a significant cause of potentially fatal infection in persons with weakened immune systems, such as individuals with HIV/AIDS. NIAID-funded investigators have discovered an antibody that protects mice from infection with *H. capsulatum*. This monoclonal antibody sticks to a protein on the fungal surface and helps the host's immune cells to destroy the fungus. This is the first demonstration of the use of an antibody for protection against infection with this fungus.

*Future Directions in Fungal Diseases Research*

In FY 2006, NIAID will support basic and applied mycology research. Research areas include: molecular biology, immunobiology, pathogenesis, therapy, and genomics and proteomics. The

[22] U.S. Centers for Disease Control and Prevention, Final 2003 Reports of Notifiable Diseases. MMWR 53: 688-696, 2004.

*Mycology Research Units (MRUs)* bring together teams of investigators to develop and improve methods for the diagnosis, prevention, and treatment of fungal infections; three new MRUs were awarded in FY 2004. The *Bacteriology and Mycology Biostatistical and Operations Unit* and the *Bacteriology and Mycology Study Group* will continue to support clinical trials on fungal and resistant bacterial infections.

## CONFRONTING IMMUNE-MEDIATED DISEASES

The immune system is a collection of cells and proteins that works to protect the body from potentially harmful, infectious microorganisms such as bacteria, viruses and fungi and plays an important role in the control of cancer and other diseases. It also is the culprit in allergies; hypersensitivity; immunologic diseases; and the rejection of transplanted organs, cells, tissues, and medical implants. The past two decades of intensive and highly productive research on the immune system have resulted in a wealth of new information and extraordinary growth in its conceptual understanding.

### *Immune Tolerance*

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated diseases, including asthma and allergic diseases; autoimmune disorders, such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis; and rejection of transplanted organs, tissues, and cells. Tolerance induction strategies aim to selectively block or prevent deleterious immune responses, while leaving protective immunity intact. Advances in tolerance induction will provide valuable new therapeutic strategies that do not require life-long, global immunosuppressive therapy with its associated deleterious side effects, and the ability to modulate tolerance will also be important for enhancing protective immunity in response to vaccines for tumors and infectious diseases.

*Science Advances in Immune Tolerance*

*In Vitro* Expanded Regulatory T Cells Suppress Autoimmune Diabetes. Research in animal models suggests that successful tolerance induction requires the elimination of tissue-damaging cells and activation of a type of immune cell called regulatory T ($T_{reg}$) cells which modulate pathogenic immune responses. Studies further suggest that the $T_{reg}$ cell population is diminished or functionally impaired in patients and animals with autoimmune disease. It has been difficult to assess the therapeutic potential of the $T_{reg}$ cell population because it is difficult to isolate a sufficient number for study. NIAID-funded investigators recently developed an *in vitro* method for robust expansion of the $T_{reg}$ cell population. They confirmed that these cells retain their immunomodulatory activity, as evidenced by their ability to reverse new onset and chronic diabetes in a mouse model of type 1 diabetes, and to prevent islet graft rejection in the diabetic mice. Most significantly, only very small numbers of $T_{reg}$ cells specifically reactive to a self protein in autoimmune diabetes are needed to accomplish this reversal of disease. Increased numbers of $T_{reg}$ cells will allow further study of their characteristics, mechanisms of action, and application to other models of immune-mediated diseases, such as graft rejection and graft-versus-host disease. Ultimately, *in vitro* $T_{reg}$ cell expansion and reinfusion into patients may be used to treat a variety of immune-mediated diseases.

*Future Directions in Immune Tolerance Research*

NIAID will continue to support research on the induction, maintenance, and loss of tolerance. These efforts will focus on: understanding the basic mechanisms of immune tolerance; manipulating the immune response for tolerance induction; and evaluating tolerance induction regimens in transplantation and autoimmune disease models. NIAID, in conjunction with the

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International (JDRF), supports the *Immune Tolerance Network (ITN),* an international consortium of over 80 investigators dedicated to the clinical evaluation of novel, tolerance-inducing therapies; the ITN will be recompeted in FY 2006. NIAID also plans to recompete the *Innovative Grants on Immune Tolerance* program in FY 2006.

### *Autoimmune Diseases*

Autoimmune diseases result from a dysfunction of the immune system in which the body attacks its own organs, tissues, and cells. The body has safeguards to prevent the immune system from attacking its own tissues, but when these safeguards are breached, an autoimmune disease can result. Medical science has identified more than 80 clinically distinct autoimmune diseases, including systemic lupus erythematosus, type 1 diabetes, severe lupus nephritis, Sjögren's syndrome, Crohn's disease, and multiple sclerosis. Collectively, autoimmune diseases afflict an estimated five to eight percent of the U.S. population and disproportionately affect women[23].

#### *Scientific Advances in Autoimmune Diseases*

Early Autoantibodies Serve as Warning for Lupus. Systemic lupus erythematosus (SLE) is a potentially life-threatening autoimmune disease that can harm the kidneys, lungs, central nervous system, and heart. Because autoantibodies are central to this damage, scientists believe that their development coincides with or precedes clinical disease. NIAID-supported researchers recently discovered that clinical manifestations of SLE are preceded by autoimmune changes that are underway, and continue to progress, for many years before diagnosis. This study indicates that the presence of autoantibodies could be used to diagnose lupus before symptoms appear, thereby enabling clinicians to offer treatment earlier in the disease course and improve treatment outcome.

#### *Future Directions in Autoimmune Diseases Research*

NIAID supports a broad range of basic and clinical research programs in autoimmunity, including several multicenter research programs. For example, NIAID has established nine *Autoimmunity Centers of Excellence* (ACEs) that conduct collaborative basic and clinical research on autoimmune diseases. The ACEs are co-sponsored by the NIDDK and the NIH. Office of Research on Women's Health (ORWH). In FY 2006, NIAID will recompete the *Autoimmune Diseases Prevention Centers*, which are cosponsored by NIDDK, the National Institute of Child Health and Human Development (NICHD), ORWH, and JDRF. The Prevention Centers will focus on prevention of autoimmune disease before clinical onset by mechanisms other than global immunosuppression. In addition, in FY 2006, NIAID plans to recompete the *Multiple Autoimmune Diseases Genetics Consortium* and the *Stem Cell Transplantation for the Treatment of Autoimmune Diseases* program.

### *Asthma and Allergic Diseases*

Allergic diseases and asthma are major causes of illness and disability in the United States; more than 50 million Americans suffer from allergies, asthma, or both, and the cost to the health care system is more than $18 billion annually[24]. An allergy is a specific reaction of the body's immune system to a normally harmless substance, one that does not bother most people. Allergic antibodies initiate allergic inflammation, rhinitis, and asthma.

[23] U.S. Department of Health and Human Services, National Institutes of Health, *Autoimmune Diseases Coordinating Committee, Autoimmune Disease Research Plan. Bethesda*, MD, 2002.
[24] NIAID, *Allergy Statistics,* http://www.niaid.nih.gov/factsheets/allergystat.htm, (accessed December 4, 2004).

*Scientific Advances in Asthma and Allergic Diseases Research*

Chronic Sinusitis Sufferers Have Enhanced Immune Responses to Fungi. Nearly 30 million people were diagnosed with sinusitis in 2002, and direct costs of the illness exceed $5.6 billion per year[25]. Scientists supported by NIAID discovered that people with chronic sinus inflammation, many of whom also suffer from allergies and asthma, have an exaggerated immune response to common airborne fungi. By comparing blood samples and nasal secretions taken from people diagnosed with chronic sinusitis with samples from healthy volunteers, the investigators observed that the levels of fungal proteins in nasal secretions were similar in both groups, thus indicating that the mere presence of fungi in the airways is not enough to cause sinusitis. The investigators also looked for evidence that immune cells from people with sinusitis respond abnormally to harmless fungi. They found that the immune cells of chronic sinusitis sufferers released significantly greater amounts of three immune-modulating chemicals called cytokines than healthy volunteers. This study is the first to show a possible immunologic basis for chronic sinusitis.

Customized Program Reduces Asthma Symptoms in Inner-City Children**.** Results from the Inner-City Asthma Study, which was co-funded by NIAID and the National Institute of Environmental Health Sciences, demonstrated that an environmental intervention that targets allergens and tobacco smoke in the home resulted in fewer asthma symptoms in children participating in the program than in those who did not. The environmental intervention, which was specifically tailored to each child's needs, substantially lowered levels of cockroach and house dust mite allergens, and investigators observed a direct relationship between reduction in allergen levels and a decline in asthma symptoms.

*Future Directions in Asthma and Allergy Research*

NIAID has been at the forefront of many advances and discoveries leading to the characterization of asthma and allergic diseases as immunological disorders. In FY 2006, NIAID will continue to support several ongoing research programs. For example, the network of 13 *Asthma and Allergic Diseases Research Centers* (AADRCs), which will be recompeted in FY 2006, conducts basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases. The *Inner-City Asthma Consortium: Immunologic Approaches to Reduce Asthma Severity*, which was initiated in FY 2002, is a network of basic scientists and clinical investigators who are evaluating the efficacy of immune-based therapies for reducing asthma severity and preventing onset in inner-city children. NIAID plans to establish the *Food Allergy Research Consortium* in FY 2005 to provide critical information on the pathophysiology and natural history of the disease and develop effective preventive interventions.

***Transplantation***

According to the Organ Procurement and Transplantation Network, more than 25,000 solid organ transplants were performed in the United States in 2003[26]. In addition, as of August 2004, more than 86,000 people had their names on waiting lists for organs such as livers, kidneys, hearts, lungs, and intestines[27]. Although organ replacement prolongs survival for people suffering from end-stage organ failure, it rarely restores normal life expectancy and can

[25] U.S Centers for Disease Control and Prevention, *Chronic Sinusitis,* http://www.cdc.gov/nchs/fastats/sinuses.htm (accessed December 4, 2004)

[26] The U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients, *2003 OPTN/SRTR Annual Report*, http://www.optn.org/AR2003/default.htm, (accessed December 4, 2004).

[27] Ibid.

sometimes lead to health problems associated with long-term use of immunosuppressive drugs, which reduce the risk of transplant rejection but also weaken the immune system against disease. Hematopoietic cell transplantation (HCT), the transplantation of stem cells found in bone marrow and cord blood, is used to treat many forms of hematologic malignancies, non-malignant diseases, and inborn errors of immunity and metabolism. Over 17,000 patients received HCT procedures in 2003[28]. However, HCT carries the risk of potentially fatal complications, such as graft failure, opportunistic infections, and graft-versus-host disease.

*Scientific Advances in Transplantation*

A Protective Gene for Graft-Versus-Host Disease following Bone Marrow Transplantation. Hematopoietic cell transplantation is an effective therapy for a number of life-threatening diseases, including leukemias. The primary complication of HCT is graft-versus-host disease (GVHD), in which donor immune cells called T cells that accompany the transplanted blood cells produce an immune response against host organs and tissues, often with fatal consequences. In a study of nearly 1,000 recipients of HCT from unrelated donors, NIAID-funded researchers discovered that a genetic variant of the gene encoding the immune system molecule interleukin-10 decreases the risk of acute GVHD and death after HCT by close to 50 percent.

*Future Directions in Transplantation Research*

In FY 2006, NIAID will continue to support transplantation research aimed at: understanding the mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues, and cells; evaluating promising therapies to improve graft survival and function and to prevent and treat graft rejection; and exploring the challenges to xenotransplantation, the transplantation of an organ, tissue, or cells between two different species. The *Clinical Trials in Organ Transplantation* program, co-sponsored by NIAID, NIDDK, and NHLBI, supports a clinical consortium dedicated to improving the success of organ transplantation. In FY 2005, NIAID will launch the *HLA Region Genetics in Immune-Mediated Diseases* initiative to continue research on defining associations between genes or markers in the HLA region and immune-mediated diseases. The genes that encode the HLA help regulate several aspects of the immune response and code for "self" markers on all body cells.

***Primary Immunodeficiency Diseases***

Primary immunodeficiency diseases are caused by inherited defects in the immune system that increase susceptibility to infections. Unlike secondary or acquired immune deficiency diseases, which are caused by infectious, chemical, or radiological agents, the estimated 80 primary immunodeficiency diseases are inherited conditions in which specific cells of the immune system do not function properly. Approximately 25,000 to 50,000 Americans are severely affected by primary immunodeficiency diseases, and there are believed to be another 500,000 persons who remain undiagnosed[29].

*Scientific Advances in Primary Immunodeficiency Diseases*

Thymus Tissue Transplantation Restores Immune System Function. DiGeorge syndrome is a congenital primary immunodeficiency disorder in which the thymus gland, heart, and parathyroid glands fail to develop normally. The thymus gland is required for the normal development and maturation of T lymphocytes, a type of immune cell. NIAID-funded researchers previously demonstrated that thymus transplantation is an effective therapy for

[28] Ibid.

[29] NIAID, *Primary Immune Deficiency*, http://www.niaid.nih.gov/factsheets/pid.htm#more, (accessed December 3, 2004).

patients with complete DiGeorge syndrome, a disorder characterized by the lack of a thymus. These researchers have extended their previous studies to include infants with partial DiGeorge syndrome, in which thymus development and function are impaired, but a small number of T cells are present. Because there was no tissue matching between the thymus donor and the infant and because the small number of T cells that remain in partial DiGeorge syndrome infants increase the risk of graft rejection, the infants were given T cell depleting agents prior to transplantation. One year post transplant, T cell function showed normal or greatly improved results as compared with the pre-transplant period, demonstrating that host T cells can proliferate and mature in a non-matched donor thymus, even after the use of T cell depleting agents. These results may also have important implications for patients requiring T cell depleting therapies for a variety of diseases.

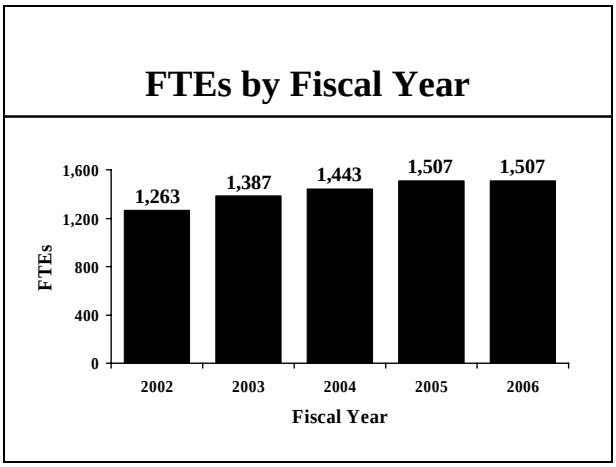
*Future Directions in Primary Immunodeficiency Diseases Research*
The major goals of NIAID-supported research in primary immunodeficiency diseases are: to understand the causes and immune mechanisms leading to their development, including identifying gene mutations and other contributing factors; to expand the genetics knowledge base to improve diagnosis, facilitate genetic counseling and decision-making for affected individuals; and to provide protective and curative treatments, including gene therapy. In FY 2006, NIAID, in conjunction with NICHD, will continue to support the *Primary Immunodeficiency Research Consortium*, a coalition of the world's most prominent researchers in the field of primary immunodeficiency diseases who are working to prioritize and coordinate future research directions and develop new resources for the study of these comparatively rare disorders.

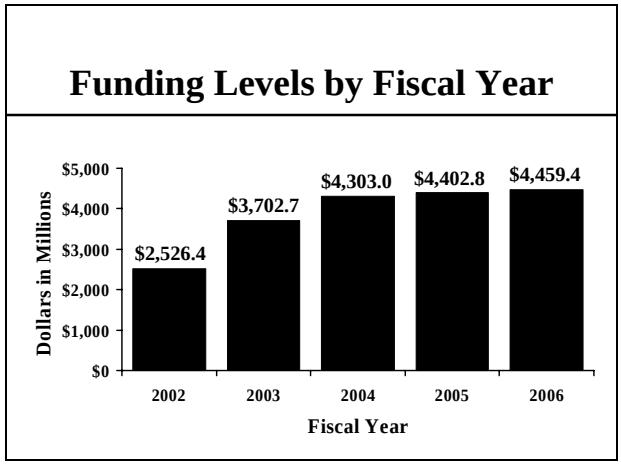
**NIH ROADMAP: ACCELERATING MEDICAL RESEARCH PROGRESS**
NIAID will explore novel approaches for diagnosis, treatment and prevention of disease using innovative research technologies such as nanomedicine, high throughput molecular screening, metabolomics, and bioinformatics through the NIH Roadmap. The Roadmap will enable NIAID to accelerate the translation of basic research discoveries into clinical practice by fostering interdisciplinary research and training and promoting public-private partnerships. The *Director's Pioneer Award* will support individual scientists with highly innovative ideas and approaches to contemporary challenges in biomedical research. Through this award, NIAID will support the study of novel approaches to HIV/AIDS vaccine development. Nanomedicine initiatives will support highly specific medical intervention at the molecular level. The Roadmap will support studies on nanomedicine immunomodulation, interdisciplinary research on antimicrobial resistance, vector-borne disease control in urban environments, and research centers – the *Exploratory Centers for Interdisciplinary Research and an Exploratory Center for Vaccinology Research*. The Berkeley Nanomedicine Center in Membrane Signaling may uncover mechanisms of immune regulation. *High Throughput Molecular Screening Assay Development* will encourage the development and automation of biological assays that enable high throughput screening (HTS) of thousands of distinct chemical entities to better understand biological processes and identify promising therapeutics. Examples of Roadmap funded HTS activities that support NIAID's mission include identification of host factors important for Listeria infection, cellular regulators of hepatitis C virus infection, and potential inhibitors for both smallpox and malaria.

## Budget Policy

The Fiscal Year 2006 budget request for the NIAID is $4,459,395,000, an increase of $56,554,000 and 1.3 percent over the FY 2005 Appropriation. Also included in the FY 2006 request, is NIAID's support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the FY 2006 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIAID are shown in the graphs below.




NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $675,160. However, the NIAID average cost for competing RPGs is skewed by the large average cost of HIV/AIDS Clinical Trials Networks. Excluding these large grants, the average cost of comparable competing RPGs is $390,242 and is at the FY 2005 level. While no inflationary increases are provided for direct, recurring costs in noncompeting RPGs, where the NIAID has committed to a programmatic increase in an award, such increases will be provided.

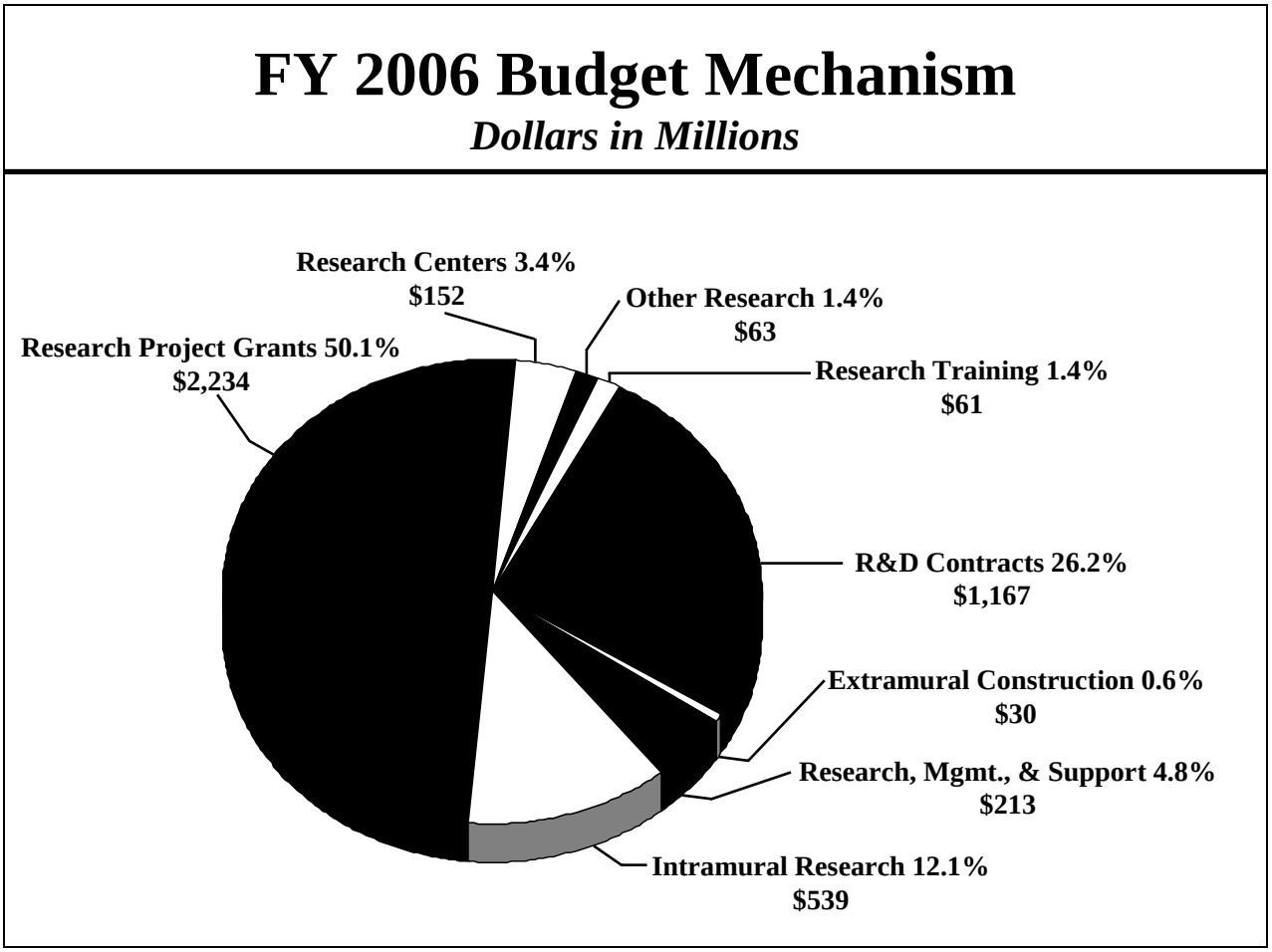
Advancement in medical research is dependent on attracting, training, and retaining the best and the brightest individuals to pursue careers in biomedical and behavioral research. In the FY2006 request, most stipend levels for individuals supported by the Ruth L. Kirschstein National Research Service Awards are maintained at the FY2005 levels. To help prevent the potential attrition of our next generation of highly trained post-doctoral trainees, stipend levels for post-docs with 1-2 years of experience are increased by 4.0%. This will bring these stipends closer to the goal NIH established for post-doc stipends in March, 2000. In addition, individual post-doctoral fellows will receive an increase of $500 in their institutional allowance for rising health benefit costs. The need for increased health benefits is particularly acute for these post-doctoral trainees, who, because of their age and stage of life are more likely to have family responsibilities. The increases in stipends and health insurance are financed within the FY2006 request by reducing the number of Full-Time Training Positions, because NIH believes that it is

important to properly support and adequately compensate those who are participating in these training programs, so that the programs can continue to attract and retain the trainees most likely to pursue careers in biomedical, behavioral and clinical research.

The Fiscal Year 2006 request includes funding for 44 research centers, 450 other research grants, including 362 research career awards, and 271 R&D contracts. Intramural Research and Research Management and Support receive increases of 1.6 percent and 1.7 percent, respectively.

Additionally, the FY 2006 budget request includes $34.0 million to support the expansion of the extramural HIV Vaccine Research Center (VRC). At the G-8 Summit in June 2004, President Bush endorsed the establishment of a Global HIV Vaccine Enterprise, a virtual consortium to accelerate HIV vaccine development, and urged his G-8 counterparts to increase their commitment to the development of an HIV vaccine. Conceptually, the extramural VRC will function similarly to the NIAID Vaccine Research Center, but will be established within the extramural community and be virtual in nature (i.e., we will not build a discrete building to house the center as we did with the NIAID VRC).

The mechanism distribution by dollars and percent change are displayed below:



# FY 2006 Estimate
# Percent Change from FY 2005 by Mechanism